REMARKS

The present application is a continuation application under 37 CFR 1.53 of Serial No. 09/269,720, filed April 6, 1999. The present remarks are in response to the Office Action mailed May 23, 2001.

The claims have been rewritten to recite that the fragment "consists of" rather than "comprises" a plasminogen fragment. It is believed that this change obviates the rejection under 35 U.S.C. 101.

New claims 1-4 include the term "naturally occurring plasminogen", which term should not be objectionable.

With respect to an "optional pharmaceutically acceptable carrier", it is respectfully submitted that this is a very common way of claiming a pharmaceutical composition which contains an active ingredient and which may or may not contain a carrier. It is respectfully submitted that one skilled in the art can readily determine what is a pharmaceutically acceptable carrier.

With respect to the anticipation rejection based upon Reich et al., it should be noted that Reich et al. disclose Lys-plg and its preparation from naturally occurring molecular species Glu-plasminogen by the catalytic activity of plasmin. Reich et al. also teach that amino-plasminogen is derived from either Glu- or Lys-plg by limited proteolysis, catalyzed by pancreatic elastase, whereby a fragment

consisting of the enzyme domain of plasminogen with a single attached Kringle is generated (column 8, lines 52-56).

In contrast thereto, the fragment of the present invention requires that there by a specific N-terminal structure of lysine-78 and absence of glycosylation. Reich et al. are silent with respect to degree of glycosylation of the plasminogen fragments, as well as any high-order structures. While it is conceded that the ultimate use of the fragments does not impart patentability thereto, it should be noted that the fragments of the present invention can be used for tumor metastasis and tumor growth. As has been demonstrated previously, lack of glycosylation and heparin binding activity is not an inherent quality of the recovered compounds. The recovered compounds include plural molecular species of Lys-LBS-I, depending upon the presence and absence of glycosylation and high-order structure. Thus, to obtain the Lys-LBS-I of the present invention, the compounds must be screened based on their ability to bind to heparin. Accordingly, Reich et al. never teach or suggest the particular Lys-LBS-I which inherently exhibits heparin binding activity and which is capable of inhibiting tumor metastasis and tumor growth.

Folkman et al. also do not teach or suggest the presently claimed fragment. Folkman et al. disclose endothelial inhibitors, called "angiostatin", which reversibly

inhibit proliferation of endothelial cells. The Folkman et al. angiostatin has been shown to inhibit the growth of endothelial cells *in vitro*. Folkman et al. define "angiostatin fragments" as protein derivatives of angiostatin, or plasminogen, which inhibit endothelial cell proliferation (column 41, lines 18-20). Folkman et al. also disclose that lysine binding site I, or angiostatin, is a population of proteins that contain, in the aggregate, at least the first three triple-loop structures (number 1 through 3) in the plasmin A-chain (Kringle 1+2+3)(column 33, lines 32-38). The molecular species of Folkman et al. **inhibits endothelial cell proliferation, which is the mechanism by which it inhibits tumor metastasis.**

In contrast thereto, the fragment of the present invention **does not inhibit endothelial cell proliferation.** If the fragment of the present invention does not function in the same way as the Folkman et al. protein, how can there possibly be anticipation?

The present inventors have demonstrated that commercially available angiostatin (angiogenesis inhibitor K1-3, Technoclone, Inc., *Blood*, 1998), Glu-LBS-I, could effectively inhibit growth of endothelial cells of blood vessels. Lys-LBS-I of the present invention **did not exhibit this activity, even at a concentration of 10- to 20-fold higher than that of angiostatin.** This is clearly shown in

Declaration 2 of Wataru MORIKAWA, submitted with the amendment filed September 11, 2000.

Likewise, the presently claimed invention is neither taught nor suggested by Davidson. Davidson discloses an isolated Kringle 5 of mammalian plasminogen, and a compound for treating antigenic diseases, methods, and compositions using this Kringle 5. It is quite clear that Davidson's Kringle 5 is not at all the same as the fragment consisting of Kringle 1 to Kringle 3 of the present invention. While Davidson does disclose producing angiostatin by elastase digestion of Lys-plg, this is merely a citation of the Folkman et al. technique and explains the various disadvantages associated with several conventional angiogenesis inhibitors.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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